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Coagulase-negative staphylococcal bloodstream infections: Does vancomycin remain appropriate empiric therapy?

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Summary *Objectives:* It is unknown if vancomycin minimal inhibitory concentrations (MICs) have increased in coagulase-negative staphylococci (CoNS) or whether vancomycin remains appropriate empiric therapy.
Methods: We performed a retrospective study at a single tertiary care center over 8 years. Adult inpatients with ≥2 positive blood cultures for CoNS within a 48-h period were eligible. Susceptibilities were performed by automated broth based-microdilution. Changes in antimicrobial susceptibility were analyzed using logistic regression. The clinical characteristics and outcomes of patients with bloodstream infections (BSI) were compared by MIC.
Results: Of 308 episodes of possible CoNS bacteremia, the vancomycin MIC was ≤1 μg/mL in 80 (26%) isolates, 2 μg/mL in 223 (72.4%) isolates and 4 μg/mL in 5 (1.6%) isolates. No isolates were resistant. We observed an 11-fold increased chance of having an isolate with a vancomycin MIC ≤1 μg/mL in 2009–2011 compared with 2004–2008 (OR 10.8, 95% CI 6.0–19.5, $p < 0.05$). In 152 patients with BSI, the median days of bacteremia, hospital mortality and readmissions at 30 days were similar in BSI caused by isolates with high vancomycin MICs (2–4 μg/mL) and low vancomycin MICs (≤1 μg/mL).

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Conclusions: We conclude vancomycin is still appropriate empiric therapy for CoNS BSIs. CoNS vancomycin MICs decreased over the study period despite widespread use of vancomycin.

Introduction

Coagulase-negative staphylococci (CoNS) have emerged as an important cause of nosocomial infections. They are the leading cause of central line,[1] pacemaker and implantable cardioverter device infections,[2] and the second most common cause of prosthetic joint infections[3] and prosthetic valve endocarditis.[4,5] With the growing use of medical indwelling devices,[5] the incidence of CoNS infections is likely to increase.

Glycopeptide antimicrobials have become first-line therapy for staphylococcal infections due to high rates of methicillin resistance.[6] For *Staphylococcus aureus*, several studies have documented a rise in vancomycin minimal inhibitory concentrations (MIC),[7,8] called "MIC creep", thought to be the result of selective pressure exerted by the increasing use of vancomycin. Infections caused by *S. aureus* isolates that are susceptible but with increased vancomycin MIC values of $\geq$1.5 μg/mL have been associated with worse clinical outcomes and higher treatment failures with vancomycin therapy than those caused by more susceptible isolates.[9] National guidelines recommend using alternatives to vancomycin when isolates have MIC values >2 μg/mL.[10]

At our institution, after several cases of severe CoNS infections caused by isolates with higher, but still susceptible, vancomycin MICs, we were concerned a similar phenomenon was occurring among CoNS. The CoNS MIC breakpoint for intermediate susceptibility is 8 μg/mL but there are few published studies evaluating the antimicrobial susceptibility trends for CoNS or whether clinical outcomes differ at lower MICs (<2 μg/mL), comparable to that found with *S. aureus*. In this study, we sought to describe the distribution of vancomycin MICs among CoNS isolates during an 8-year period and to compare the outcomes of bloodstream infections (BSI) caused by isolates with vancomycin MICs of $\leq$1 μg/mL with infections caused by isolates with vancomycin MICs of $\geq$2 μg/mL.

Patients and methods

Study design

We conducted a retrospective cohort study of patients admitted to Boston Medical Center between January 2004, when electronic medical records became available, and December 2011. Adult patients with 2 or more positive blood cultures for CoNS within a 48-h period were eligible for the study and were labeled "possible CoNS bacteremias". Patients were excluded if they were younger than 18 years, survived less than 24 h after the index blood culture was obtained, remained inpatients for less than 24 h, or had other microorganisms isolated concomitantly with CoNS. Only the first episode was included for patients with more than one possible CoNS bacteremia because subsequent episodes could not be classified as independent events e.g. if underlying comorbidity, retained devices, or intrinsic skin microflora were contributory.

Trends in the proportion of CoNS isolates with vancomycin MIC $\leq$1 μg/mL and the susceptibility of isolates to oxacillin, levofloxacin, gentamicin and trimethoprim-sulfamethoxazole (TMP-S) during the study period were evaluated.

BSIs caused by CoNS isolates with vancomycin MICs $\geq$2 μg/mL were compared with those caused by isolates with MICs $\leq$1 μg/mL to examine clinical characteristics and outcomes. We included those episodes of CoNS bacteremia that met the 2008 Center for Disease Control and Prevention (CDC) definition for BSI i.e. 2 or more positive blood cultures for CoNS with no more than one calendar day gap between isolates and more than one of the following clinical criteria: temperature $\geq$38.3 °C, presence of chills, or a systolic blood pressure below 90 mmHg with no other source of infection. Use of those criteria resulted in fewer cases for analysis compared to blood cultures analyzed by microbiological criteria. Patient factors (age, gender, comorbidities, location in the intensive care unit, presence of fever, hypotension and leukocytosis defined as more than 10,000 white blood cells/mm^3 at the time the blood culture was obtained, vancomycin exposure in prior 3 months, antibiotic treatment of BSI) and outcomes (median days of bacteremia, hospital length of stay, hospital mortality and readmission rates) for all CoNS BSI and for those treated with vancomycin were analyzed. Antibiotic data was only available if therapy was prescribed at the study hospital.

Microbiological methods

The recovery of blood isolates was performed using one of two automated blood culture systems: VersaTREK (TREK Diagnostic) prior to May 2011 and BacT/ALERT 3D (bioMérieux, Inc.) after May 2011. Except for *S. lugdunensis* after April 2005, CoNS isolated from blood cultures were not routinely speciated. Microbiology susceptibility tests were performed by automated instrumentation using contemporaneous CLSI (formerly NCCLS) breakpoints.[11] The platform for antimicrobial susceptibility testing changed from VITEK Legacy (bioMérieux, Inc) to VITEK 2 (bioMérieux, Inc.) in February 2008. VITEK 2 test panels were changed from AST GP66 to AST GP67 in October 2008. In each case, successful comparative verifications of the predicate and new system or panel were performed by the laboratory; there were no issues regarding agreement of vancomycin MICs. For the present analysis, vancomycin MICs were grouped by MICs $\leq$1 μg/mL and MIC $\geq$2 μg/mL because VITEK panels used prior to the AST GP67 panel did not discriminate vancomycin MICs below 1 μg/mL.

In cases in which there was one 2-fold dilution MIC difference between 2 index isolates (considered to be